Inter-dependency between Akt-1 and heme oxygenase-1 in the regulation of soluble Endoglin

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Endothelial dysfunction is a hallmark of preeclampsia. Desensitization of the phosphoinositide 3-kinase (PI3K)/Akt pathway underlies endothelial dysfunction and heme oxygenase-1 (HO-1) is decreased in preeclampsia. To identify therapeutic targets, we sought to assess whether these two regulators act to suppress soluble endoglin (sEng), an antagonist of TGF-β signaling, which is known to be elevated in preeclampsia. VEGF-A, FGF-2, Ang-1 and insulin, which all activate the PI3K/Akt pathway, inhibited the release of sEng from endothelial cells. Inhibition of the PI3K/Akt pathway, by overexpression of PTEN or a dominant-negative isoform of Akt (Akt\textsubscript{dn}) induced sEng release in endothelial cells and prevented the inhibitory effect of VEGF-A. Conversely, overexpression of a constitutively active Akt (Akt\textsubscript{myr}) inhibited PTEN and cytokine induced sEng release. Systemic delivery of Akt\textsubscript{myr} to mice significantly reduced circulating sEng, whereas Akt\textsubscript{dn} promoted sEng release. Preeclamptic placenta has reduced phosphorylated Akt and this correlates with the elevated level of circulating sEng. Knock-down of Akt using siRNA prevented HO-1-mediated inhibition of sEng release and reduced HO-1 expression. Furthermore, HO-1 null mice have reduced phosphorylated Akt in their organs and overexpression of Akt\textsubscript{myr} failed to suppress the elevated levels of sEng detected in the plasma of HO-1 null mice, indicating that HO-1 is required for the Akt-mediated inhibition of sEng. The loss of PI3K/Akt and/or HO-1 activity, promotes sEng release and positive manipulation of these pathways offers a strategy to circumvent endothelial dysfunction.